REMARKS/ARGUMENTS

The Pending Claims

Before entry of the preceding Amendments, Claims 109-113, 115, 117-120 and 151-153 are pending in the above-captioned application. Claims 109-113, 115 and 117-120 are directed to nucleic acid probes or primers comprising nucleotide sequence of human 3'-phosphoadenosine-5'-phosphosulfate synthetase (PAPSS2). Claims 151-153 relate to genetic testing kits for diagnosing spondyloepimetaphyseal dysplasia (SEMD).

Applicants' Amendment

Applicants have amended the specification at pages 39-40 to delete "embedded hyperlink and/or other forms of browser-executable code," as requested by the Examiner. No new matter is added by the amendments.

Applicants have amended herein Claims 109-113, 115, 117-120 and 151-153 as further described below. No new matter is added by the amendments.

Claims 152-153 have been amended to insert "(SEMD)" after "spondyloepimetaphyseal dysplasia" and to delete the parentheses at the end of the word "primers" in the second paragraph, which is merely intended as a refinement for greater clarity in using the abbreviation "SEMD" in the claims. In Claim 152, the deletion of the final "s" from the word "pair" is merely for greater clarity, in view of the antecedent basis provided by the preamble of Claim 117, from which Claim 152 depends. No change in claim scope is intended by these amendments, nor is any new matter added thereby.

Applicants have amended the drawings (*see* Amendment to Drawings, page 8). No new matter is added by the amendments. Applicants have attached sheets of drawings that include formal renderings of Figures 1-4.

The Office Action and Applicants' Response

The Examiner acknowledged Applicants' Response to the restriction requirement in which Group I was elected without traverse.

The Examiner required deletion of the embedded hyperlink and/or other form of browser-executable code in the disclosure. Accordingly, Applicants submit herein with Amendments to the Specification (*see* page 2).

The Examiner required response to the "Notice to Comply", which notifies that the computer readable form (CRF) of the sequence listing could not be processed by the Scientific and Technical Information Center (STIC) for the diskette was melted. Accordingly, Applicants submit herewith a substitute sequence listing in computer readable form together with a paper copy and statement under 37 C.F.R. § 1.821 (f) and (g) concerning same.

No claims were allowed. The following grounds of rejections were cited by the examiner.

A. Rejection under 35 U.S.C. § 112

The Examiner rejected Claims 109-113, 115, 117-120 and 151-153 under **35 U.S.C. § 112, first paragraph**. The Examiner stated the following reasons:

The claims are drawn to nucleic acid sequences, primer pairs, and kits comprising such. The recitation of nucleic acid sequences "comprising", sequences "complementary", "gene specific fragments", and "PAPSS2 specific nucleic acids" encompasses an extremely large number of genomic sequences, mutants, variants, and homologs of human PAPSS2 which have not been taught or described in the specification. The specification teaches the sequence of SEQ ID NO 1, which is the sequence of human PAPSS2. The claims, however, only recite sequences from within SEQ ID NO:1, wherein sequences "comprising", "complementary", "gene specific fragments" and PAPSS2 specific fragments of this minimal recitation of contiguous nucleotides within SEQ ID NO 1 or SEQ ID NOS 3-6, 11-18 and 28 encompass genomic sequences, as well as mutants, variants and homologs of human PAPSS2 which have not been taught or described by the specification. The specification does not define the term "PAPSS2" such that the skilled artisan would be able to determine what constitutes a PAPSS2 specific nucleic acid. Further, the specification does not define the term "complimentary". As such, the term has been broadly interpreted to encompass sequences which need only have some degree of complementarity to the recited sequences. These recitations, along with the terms "comprising" and "gene specific fragments" encompass a large genus of nucleic acids. However, the disclosure of the human and mouse PAPSS2 cDNA represent a species of this extremely large genus of nucleic acids and is not representative of this large genus.

Applicants have amended Claims 109-113, 115, 117-120 and 150 to insert "fully" before "complementary" to clarify the degree of complementarity required in accordance with the claimed invention. Support for these amendments is found in the specification as originally filed, *e.g.*, at page 18, line 32 through page 19, line 1; and at page 19, lines 26-28.

Applicants have also amended Claims 109-113, 115, 120 and 151 to delete the recitations of "gene-specific fragment" and/or "a PAPSS2-specific sequence overlapping either of these at 5 or more contiguous nucleotides at its 5' or 3' end".

Additionally, Applicants have further amended Claim 109 by inserting the recitation of particular fragments of SEQ ID NO:1. In particular, amended Claim 109 relates to nucleotide sequences [SEQ ID NOS: 1, and 3-6] that are described in the specification (*see, e.g,* at page 19, lines 12-17), and fully complementary and/or degenerate coding sequences of these.

Amended Claims 115, 118-120 and 151 are directed, *inter alia*, to PAPSS2-specific fragments of SEQ ID NO:3, 5-6, 11-18 and 28 at least 15 nucleotides long. Claim 117 is directed to "a PAPSS2 gene-specific fragment" of (SEQ ID NO:1) or (SEQ ID NO:9) or "a nucleotide sequence fully complementary to any of" SEQ ID NO:1 or 9. Applicants disagree with the Examiner's assertion that "[t]he specification does not define the term 'PAPSS2' such that the skilled artisan would be able to determine what constitutes a PAPSS2 specific nucleic acid." The specification as originally filed defines PAPSS2 as follows: "The present invention relates to an isolated polynucleotide or to a nucleic acid construct that comprises a nucleic acid segment encoding a 3'-phosphoadenosine-5'-phosphosulfate (PAPS) synthetase (PAPSS), particularly, a human PAPSS2 nucleotide sequence of (SEQ ID NO:1)..." (*See, e.g.,* at page 9, lines 17-20). The specification further teaches that (SEQ ID NO:1) includes 5' non-coding region and promoter of PAPSS2 sequence, where nucleic acid segment encoding PAPSS2 "comprises a nucleotide sequence defining an open reading frame within SEQ ID NO:1 that extends from nucleotide position +1 through +1845 (SEQ ID NO:9)." (*See,* at page 11, lines 19-32 to page 12, lines 1-23).

Based on the teachings of specification as originally filed and the general knowledge in the art, it would have been clear to the skilled artisan what constitutes a PAPSS2-specific nucleic acid. The specification lists examples of useful oligonucleotide primer sequences for amplifying PAPSS2-specific nucleic acid segments including primer sequences SEQ ID NOS: 3-6, 11-18 and 28 (*see, e.g.,* at page 19, lines 12-26). The specification also states, "Most preferably, amplification of the subject's nucleic acids can be achieved using *PAPSS2*-specific oligonucleotide primers and primer pairs of the present invention, as described above. For example, useful primers comprise a nucleotide sequence of (SEQ ID NOS:3-6, 11-18, or 28) or a *PAPSS2*-specific fragment of any of these at least 15 nucleotides long . . ." (*See,* at page 27, lines 22-26 of the disclosure).

Additionally, the specification defines "gene-specific fragment" as "nucleic acid segments having a contiguous sequence that is specific to PAPSS2" and cites as examples various BLAST programs known to the skilled artisan for distinguishing gene-specificity (*e.g.*, at page 14 , lines 7-18 of the disclosure). Thus, the skilled artisan would be able to determine a "PAPSS2-specific" or "PAPSS2 gene-specific" nucleic acid, based on the disclosure of the specification and the general knowledge in the art.

In view of the amendments to Claims 110-111, 115, 117-120 and 151, Applicants believe the rejection of Claims 109-113, 115, 117-120 and 151-153 is overcome. Therefore, Applicants respectfully request the Examiner to withdraw the rejection on this ground.

B. Rejections Under 35 U.S.C. § 102

(1) The Examiner rejected Claims 109-113 and 115 under **35 U.S.C. § 102(b)** as being anticipated by **Brennan** [U.S. Patent No. 5, 474,796 (12/1996)]. The Examiner stated the following reasons:

> **The claims are drawn to nucleotide sequences complimentary to, SEQ ID NO:1 or degenerate coding sequences thereof, or gene specific fragments, or sequences that minimally contain 5 contiguous sequences of SEQ ID NOS:3-6. As the claims do not recite any upper length limitations and do not define the terms "gene specific fragment" or PAPSS2 specific nucleotide sequence, the claims encompass a large number of possible 10 mer nucleic acid sequences. Brennan teaches making every possible 10 nucleic acid sequences (see example 4, col. 9), many of which are encompassed by the instant claims.**

Applicants have amended Claims 109-113 and 115 to delete recitations that are directed to a "gene-specific fragment" and a "PAPSS2-specific nucleotide sequences overlapping at 5 or more contiguous nucleotide positions any sequence of" SEQ ID NOS:3-6 (*see* Amendments to Claims, pages 3-4). Further, Applicants have inserted "fully" before "complementary" to clarify the degree of complementarity required.

Amended Claims 109-113 and 115 are directed to sequences [SEQ ID NOS:1, 3-7, 11-18 and 28] that comprise of 20 or more nucleotides. Therefore, Brennan does not anticipate the claims because Brennan only teaches making every possible 10-nucleic acid sequence and not the recited sequences.

In view of the amendments to Claims 109-113 and 115, Applicants believe the rejection of these claims is overcome. Therefore, Applicants respectfully request the Examiner to withdraw the rejection on this ground.

(2) The Examiner also rejected Claims 109-113, 115 and 117-120 under **35 U.S.C. § 102(a)** as being anticipated by **Haque *et al.*** [Nat. Genet. 20(2), 157-162 (Oct. 1998)]. The Examiner stated the following reason: "Haque teaches primer sequences (*see* p. 161, col 2: 'Radiation hybrid mapping' and 'Mutation analysis') which are identical to SEQ ID NOS: 3-6, and anticipates limitations in each of the claims."

Applicants have herein attached the Declaration under 37 C.F.R. §1.132, executed July 11, 2001 and originally filed in parent application 09/399,212 on August 8, 2001. (Appended as

Exhibit A). In his Declaration, Dr. Cohn avers that Haque *et al.*, was published less than 12 months before the priority date of the above-captioned application, was co-authored by the named inventors and that the other co-authors did not contribute to the conception of the invention. The Declaration of Dr. Daniel Cohn particularly states that the nucleic acid sequences disclosed in the cited reference, SEQ ID NOS: 1, 2 and 9, are part of the claimed technology in Ser. No. 09/399,212 (the parent application of the above-captioned application, filed on September 17, 1999, subsequently abandoned) and that only the named co-inventors, Daniel Cohn, Muhammad Faiyaz ul Haque, Lily King, and Deborah Krakow, participated in the identification of nucleotide sequences claimed in Ser. No. 09/399,212 and now in the above-captioned 09/898,165. (**Exhibit A at ¶ 6**). Additionally, Dr. Daniel Cohn's declaration states that the other co-authors listed on the article, *i.e.*, Rita Cantor, Mike Rusiniak, Richard Swank, Andrea Superti-Furga, Sayedul Haque, Hawssan Abbas, Wasim Ahmad, and Mahmud Ahmad, were not and are not co-inventors of the claimed invention. (**Exhibit A at ¶ 8**).

Therefore, the cited reference is eliminated as properly citable art against the claimed invention, under 35 U.S.C. § 102(a). Accordingly, Applicants respectfully request the Examiner to withdraw the rejections on this ground.

(3) Claims 109-113, 115 and 117-120, under **35 U.S.C. § 102(b)**, were also rejected by the Examiner as being anticipated by **Kurima *et al.*** [PNAS, 95:8681-8685 (July 1998)]. The Examiner stated the following reasons:

> **Kurima teach the nucleotide sequence of murine SK2, which is 85.6% identical to SEQ ID NO:1 over nucleotides 92-1924 (see attached sequence alignment). As the claims do not recite an upper or lower length limitation or define 1) the degree of complementarity to SEQ ID NO:1, 2) what a gene specific fragment of SEQ ID NO:1 encompasses, or 3) what constitutes a PAPSS2 specific nucleic acid sequence, the nucleotide sequence of murine SK2 anticipates the nucleic acids of claims 109-113 and 115. Further, Kurima teaches nucleic acid primers for amplification (see p. 8682, 2nd col. First full para) which contain sequences complimentary (albeit not the full complement) to the claimed nucleic acids. Such sequences have been broadly interpreted to encompass "gene specific fragments" and "PAPSS2 specific nucleic acid sequences".**

Applicants have amended Claims 109-113, 115 and 117-120 to delete recitations that are drawn to a "gene-specific fragment" of SEQ ID NO:1 (*see* Amendments to Claims, pages 3-6). Applicants have inserted "fully" before "complementary" to clarify the degree of complementarity required.

Amended Claims 115 and 118-120 are directed, *inter alia*, to PAPSS2-specific fragments of SEQ ID NO:3, 5-6, 11-18 and 28 *at least 15 nucleotides long*. Claim 117 is directed to "a PAPSS2 gene-specific fragment" of (SEQ ID NO:1) or (SEQ ID NO:9) or "a nucleotide sequence *fully* complementary to any of" SEQ ID NO:1 or 9. The upper limits of length are inherently determined by the lengths of the designated sequences. These fragments are not anticipated by Kurima *et al.*'s sequences of murine SK2, which the Examiner has acknowledged are not fully complementary to the nucleic acid sequences as claimed. The specification as originally filed defines PAPSS2 as follows: "The present invention relates to an isolated polynucleotide or to a nucleic acid construct that comprises a nucleic acid segment encoding a 3'-phosphoadenosine-5'-phosphosulfate (PAPS) synthetase (PAPSS), particularly, a *human* PAPSS2 nucleotide sequence of (SEQ ID NO:1)..." (*See, e.g.,* at page 9, lines 17-20; emphasis added). The specification further teaches that (SEQ ID NO:1) includes 5' non-coding region and promoter of PAPSS2 sequence, where nucleic acid segment encoding PAPSS2 "comprises a nucleotide sequence defining an open reading frame within SEQ ID NO:1 that extends from nucleotide position +1 through +1845 (SEQ ID NO:9)." (*See,* at page 11, lines 19-32 to page 12, lines 1-23).

Additionally, the specification defines "gene-specific fragment" as "nucleic acid segments having a contiguous sequence that is specific to PAPSS2" and cites as examples various BLAST programs known to the skilled artisan for distinguishing gene-specificity (*e.g.*, at page 14 , lines 7-18 of the disclosure). Thus, based on the disclosure of the specification and the general knowledge in the art, the skilled artisan would be able to determine a "PAPSS2-specific" or "PAPSS2 gene-specific" nucleic acid, which is not anticipated by Kurima *et al.*'s murine SK2 sequence.

In view of the amendments to Claims 109-113, 115 and 117-120, Applicants believe the rejection of these claims is overcome. Therefore, Applicants respectfully request the Examiner to withdraw the rejection on this ground.

C. Rejection under 35 U.S.C. § 103

The Examiner rejected Claims 151-153 under **35 U.S.C. § 103(a)** as being unpatentable over **Haque et al.** or in the alternative, **Kurima et al.**, each in view of **Ahern** [The Scientist, vol. 9, 1995, pages 1-5 from the Internet]. The Examiner stated the following reasons:

Haque teaches primer sequences (see p. 161, col 2: "Radiation hybrid mapping" and "Mutation analysis") which are identical to SEQ ID NOS: 3-6.

Kurima teach the nucleotide sequence of murine SK2, which is 85.6% identical to SEQ ID NO:1 over nucleotides 92-1924 (see attached sequence alignment). As the claims do not recite an upper or lower length limitation or define 1) the degree of complementarity to SEQ ID NO:1, 2) what a gene specific fragment of SEQ ID NO:1 encompasses, or 3) what constitutes a PAPSS2 specific nucleic acid sequence, the nucleotide sequence of murine SK2 anticipates the nucleic acids of claims 109-113 and 115. Further, Kurima teaches nucleic acid primers for amplification (see p. 8682, 2nd col. First full para) which contain sequences complimentary (albeit not the full complement) to the claimed nucleic acids. Such sequences have been broadly interpreted to encompass "gene specific fragments" and "PAPSS2 specific nucleic acid sequences".

Neither Haque nor Kurima teach the primer pairs in kit format, however Ahern teaches that packaging biochemcial reagents in kit format save the researcher time and provides convenience (see p. 4, para 1-2). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to package the primer pairs of either Haque or Kurima in kit format, as taught by Ahern, for the purpose of making the methods of Haque or Kurima in kit format, as taught by Ahern, for the purpose of making the methods of Haque or Kurima easier and more convenient to perform. The ordinary artisan would have been motivated to package the primer pairs in kit format as Ahern teaches that packaging reagents in kit format offer scientists the opportunity to better manage their time.

Applicants assert that Haque *et al.* is not properly citable against the claimed invention, as discussed above (pages 12-13), in connection with **Exhibit A**.

Applicants have herein attached the Declaration under 37 C.F.R. §1.132, executed July 11, 2001 and originally filed in parent application 09/399,212 on August 8, 2001. (Appended as **Exhibit A**). In his Declaration, Dr. Cohn avers that Haque *et al.*, was published less than 12 months before the priority date of the above-captioned application, was co-authored by the named inventors and that the other co-authors did not contribute to the conception of the invention. The Declaration of Dr. Daniel Cohn particularly states that the nucleic acid sequences disclosed in the cited reference, SEQ ID NOS: 1, 2 and 9, are part of the claimed technology in Ser. No. 09/399,212 (the parent application of the above-captioned application, filed on September 17, 1999, subsequently abandoned) and that only the named co-inventors, Daniel Cohn, Muhammad Faiyaz ul Haque, Lily King, and Deborah Krakow, participated in the identification of nucleotide sequences claimed in Ser. No. 09/399,212 and now in the above-captioned 09/898,165. **(Exhibit A at ¶ 6)**. Additionally, Dr. Daniel Cohn's declaration states that the other co-authors listed on the article, *i.e.*, Rita Cantor, Mike Rusiniak, Richard Swank,

Andrea Superti-Furga, Sayedul Haque, Hawssan Abbas, Wasim Ahmad, and Mahmud Ahmad, were not and are not co-inventors of the claimed invention. **(Exhibit A at ¶ 8)**.

Therefore, the cited Haque *et al.* reference is eliminated as properly citable art against the claimed invention, under 35 U.S.C. § 103(a).

Applicants have amended Claims 117 and 120, from which Claims 152 and 153 depend, respectively, to delete recitations that are drawn to a "gene-specific fragment" of SEQ ID NO:1. Applicants have inserted "fully" before "complementary" to clarify the degree of complementarity required.

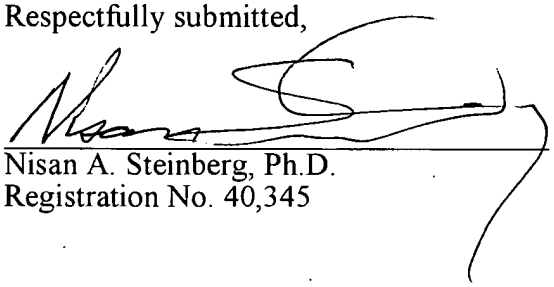
Amended Claims 117, 120 and 151 are directed, *inter alia*, to PAPSS2-specific fragments of SEQ ID NO:3, 5-6, 11-18 and 28 *at least 15 nucleotides long*. Claim 117 is directed to "a PAPSS2 gene-specific fragment" of (SEQ ID NO:1) or (SEQ ID NO:9) or "a nucleotide sequence *fully* complementary to any of" SEQ ID NO:1 or 9. The upper limits of length are inherently determined by the lengths of the designated sequences. These fragments of human *PAPSS2* sequences are neither anticipated nor made obvious by Kurima *et al.*'s sequences of murine SK2, which the Examiner has acknowledged are not fully complementary to the nucleic acid sequences as claimed. The specification as originally filed defines PAPSS2 as follows: "The present invention relates to an isolated polynucleotide or to a nucleic acid construct that comprises a nucleic acid segment encoding a 3'-phosphoadenosine-5'-phosphosulfate (PAPS) synthetase (PAPSS), particularly, a *human* PAPSS2 nucleotide sequence of (SEQ ID NO:1)..." (*See, e.g.*, at page 9, lines 17-20; emphasis added). The specification further teaches that (SEQ ID NO:1) includes 5' non-coding region and promoter of PAPSS2 sequence, where nucleic acid segment encoding PAPSS2 "comprises a nucleotide sequence defining an open reading frame within SEQ ID NO:1 that extends from nucleotide position +1 through +1845 (SEQ ID NO:9)." (*See,* at page 11, lines 19-32 to page 12, lines 1-23).

Additionally, the specification defines "gene-specific fragment" as "nucleic acid segments having a contiguous sequence that is specific to PAPSS2" and cites as examples various BLAST programs known to the skilled artisan for distinguishing gene-specificity (*e.g.*, at page 14 , lines 7-18 of the disclosure). Thus, based on the disclosure of the specification and the general knowledge in the art, the skilled artisan would be able to determine a "PAPSS2-specific" or "PAPSS2 gene-specific" nucleic acid, which is not made obvious by Kurima *et al.*'s murine SK2 sequence.

Further, the combination of Ahern with Kurima *et al.*, minus the hindsight provided by the disclosures of Applicants' specification, fails to make obvious any of the primers having (A) the designated nucleotide sequences, (B) fully complementary sequences, and/or (C) PAPSS2-specific fragments, of which the claimed kits are comprised.

Therefore, Applicants respectfully request the Examiner to withdraw the rejection on this ground.

Respectfully submitted,



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